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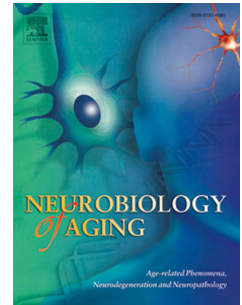
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Title: The relation of structural integrity and task-related functional connectivity in the ageing brain

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The relations among structural integrity, functional connectivity, and cognitive performance in the ageing brain are still understudied. Here we used multimodal and multivariate approaches to specifically examine age-related changes in task-related functional connectivity, gray matter volumetrics, white matter integrity, and performance. Our results are twofold, showing (i) age-related differences in functional connectivity of the working memory network and (ii) age-related recruitment of a compensatory network associated with better accuracy on the task. Increased connectivity in the compensatory network correlates positively with preserved white matter integrity in bilateral frontoparietal tracks and with larger gray matter volume of right inferior parietal lobule. These findings demonstrate the importance of structural integrity and functional connectivity in working memory performance associated with healthy ageing.

Keywords: Structural Integrity; Functional Connectivity; White Matter; Gray Matter; Age-Related Compensation.

Healthy ageing is associated with structural and functional changes in the brain, as well as a decline in behavioural performance on a variety of cognitive tasks. Efficiency of cognitive functioning necessarily depends on the integrity of cerebral gray and white matter (GM and WM); yet, little is known about the relation among age-related changes in structure, behaviour, and task-related functional connectivity (FC). Despite widespread anatomical variability, converging evidence demonstrates age-related cortical thinning and reduction in GM volume (Tisserand *et al.*, 2002), as well as a loss of integrity in WM microstructure (Guttmann *et al.*, 1998). Functionally, theories of cognitive ageing concur that two distinct phenomena take place in the ageing brain: *dedifferentiation*, *i.e.*, reduced distinctiveness of neural representations in domain-specific areas (Li *et al.*, 2001), and *compensation*, *i.e.*, over-recruitment of alternate brain circuits to compensate for age-related processing deficiencies in the existing circuitry that subserves a specific cognitive function (Cabeza *et al.*, 2002; Grady, 2012; Reuter-Lorenz *et al.*, 2000). Increased engagement of prefrontal and other brain areas is interpreted as compensatory when associated with maintained performance in older adults (Davis *et al.*, 2008; Grady, 2002; Grady *et al.*, 2002; Madden *et al.*, 2004), or when activity in these over-recruited areas is positively correlated with behaviour in older adults (Burianová *et al.*, 2013; Davis *et al.*, 2008; Grady *et al.*, 2002). It is argued that the strongest evidence for compensation is the recruitment of additional neural resources in older adults, *i.e.*, higher levels of mean activity or stronger functional connectivity, *and* that this recruitment is related to better performance in older adults (Cabeza and Dennis, 2013; Grady 2008). Whilst compensation links functional activity and behaviour, the interplay between compensation and structural integrity is still unclear. It is of

processes have been shown not to be mutually exclusive (Burianová *et al.*, 2013). Thus, the brain may show reduced neural selectivity in the domain-specific regions as well as utilize a different network of areas to compensate for this deficiency in neural distinctiveness.

Concurrent investigations of age-related alterations in structure and function are necessary because the mechanisms underlying changes in structural integrity may likely mediate changes in FC and performance on cognitive tasks. Recent studies have reported an association between age-related changes in WM microstructure and cognitive performance (Burzynska *et al.*, 2013), as well as between age-related decline in GM volume and performance (Steffener *et al.*, 2012), thereby demonstrating significant covariance between better structural integrity and higher cognitive functioning in aged adults. Although standard *in vivo* imaging methods preclude drawing of direct causal inferences regarding structure-function-behaviour relations, multimodal imaging approaches may provide convergent evidence for complex macroscopic principles that facilitate age-related plasticity.

The objective of the current study was to use multimodal imaging and multivariate analysis methods to investigate the relation among changes in FC of a task-related network, behavioural performance, and structural integrity in an ageing population. Specifically, we utilized a validated cognitive task (n-back) to delineate the working memory network, which engages essential load-dependent frontoparietal (FP) nodes (Honey *et al.*, 2002), and examined the relation between the strength of FC in this network and task performance. Older adults often compensate for deficits in posterior brain regions by increasing frontal activity (Grady *et al.*, 2002); thus, we examined GM volumetrics of the network's FP nodes and WM microstructure of their connecting WM tract, the superior longitudinal fasciculus (SLF; Petrides & Pandya, 2002).

frontal regions under low load, as ageing has been associated with increased recruitment of available frontal resources at lower levels of cognitive load (Reuter-Lorenz & Cappell, 2008); and (ii) older adults who perform better on the working memory task would recruit brain regions outside of the working memory network to aid their performance under high cognitive load, when available resources would have reached their limit. In addition to its association with more accurate performance, this compensatory recruitment would relate to greater structural integrity, as we propose that intact brain structure may play a biologically permissive role in functional compensation (Murphy & Corbett, 2009).

Methods

Participants.

Twenty three healthy older adults (mean age = 66 years, SD = 5 years, 13 females) and 22 healthy young adults (mean age = 29 years, SD = 6 years, 10 females) participated in the study. All participants were right-handed, had normal or corrected-to-normal vision, no history of neurological impairment or psychiatric illness. The two groups of participants were education-matched. Older adults were cognitively intact and achieved an average score of 28.9 (SD 1.1; range 27-30), on the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975). All participants provided written informed consent approved by the University of Queensland Human Research Ethics Committee.

Experimental Design.

Participants underwent a 45-minute experimental session, which consisted of 3

and functional MRI (fMRI). During fMRI, participants were presented with a continuous series of letters and performed an n-back task with three experimental conditions: 0-back, 1-back, and 2-back. During the 0-back condition, participants were required to press '1' if the letter 'A' was presented, or '2' if any other letter was presented. During the 1-back and 2-back conditions, participants were required to press '1' if the current letter matched the letter one or two letters earlier, respectively, or '2' if it did not match. Letters were presented in a blocked-design, with four blocks of each experimental condition, 20 letters per block, and 4-6 targets per block. Each block consisted of a 3s instruction, 500ms stimulus presentation, and 1s inter-stimulus-interval. Three 20s fixation blocks were presented at the beginning, middle, and end of each of the functional runs. Prior to the experimental session, the task was verbally and visually explained to the participants who subsequently took part in a short practice session, which ensured a proper familiarization with the task's instructions and timing.

MRI Acquisition and Analysis.

T1-weighted volumetric structural MRIs were acquired using a 3D MP-RAGE sequence (192 sagittal slices, TR = 1900ms, TE = 2.32ms, TI = 900ms, FOV = 230mm, voxel size = 0.9mm^3 , flip angle = 9°). Estimates of cortical volume were obtained using the default preprocessing steps of FreeSurfer software (<http://surfer.nmr.mgh.harvard.edu>). For each participant, brains were extracted and intensities normalized. Then, gray matter, white matter, and non-cortical structures were segmented and a triangular mesh was utilized to generate the pial and cortical surfaces, which was followed by a manual quality control check of gross structural abnormalities, occurrence of artefacts, and accuracy of registration (Dale *et al.*, 1999;

inferior parietal lobule (IPL) and the rostral division of the middle frontal gyrus (MFG) in each hemisphere, using the Desikan-Killiany atlas (Desikan *et al.*, 2006). Volume measures were normalized as percentage of total intracranial volume, to correct for difference in head size. All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS; version 21; Chicago, IL, USA). Individual values of cortical volume of the ROIs were used as covariates in task-related functional connectivity analysis (see below).

DWI Acquisition and Analysis.

High angular resolution diffusion-weighted images (HARDI) were acquired along 85 gradient directions using spiral acquisition (55 slices, TR = 9400ms, TE = 112ms, b-value = 3000s/mm², voxel size = 2.5mm³) and processed using Dipy software (Garyfallidis *et al.*, 2014; <http://nipy.org/dipy/>). DWIs were first corrected for motion and residual eddy current induced distortions using ExploreDTI software with B-matrix adjustments (Leemans & Jones, 2009; <http://www.exploredti.com/>). Then, after skull and non-brain tissue were removed from the image using median Otsu segmentation (Garyfallidis *et al.*, 2014), the tensor model was fitted to each voxel using nonlinear regression, and, finally, fractional anisotropy (FA) maps were calculated (Basser *et al.*, 1994). FA is considered a general marker of WM integrity, reflecting coherence within a voxel and fiber density (Beaulieu, 2002), yet in the absence of other diffusivity measures it is generally accepted as a nonspecific marker of microstructural change (Alexander *et al.*, 2007). To maximize specificity, we obtained additional maps of different diffusivity measures from the tensor; namely, radial diffusivity (RD), a marker of demyelination

Group differences for these diffusivity measures were assessed for the whole white matter skeleton using tract-based spatial statistics (TBSS; Smith *et al.*, 2006) included in FMRIB's Software Library (FSL; <http://fsl.fmrib.ox.ac.uk/>). All diffusivity maps, including a common white matter skeleton for all participants, were linearly co-registered to the avgMNI152 template using FSL's FLIRT (Jenkinson & Smith, 2001). The aligned individual diffusivity maps were masked with the common white matter skeleton and submitted to FSL's voxelwise permutation tool 'randomise', which conducted an unpaired *t*-test between the groups' maps (Nichols & Holmes, 2002). Five thousand random permutations for each diffusivity measure and threshold-free cluster enhancement (TFCE) were used for statistical assessment (Smith & Nichols, 2009). The resulting statistical maps were thresholded at $p < 0.05$ and corrected for multiple comparisons using family-wise error correction. Finally, average white matter values (FA, AD, RD) for bilateral SLF, the primary WM pathway connecting the frontal and parietal nodes of the working memory network (Petrides & Pandya, 1984), were derived and used as covariates in task-related functional connectivity analysis (see below). First, a tract-of-interest (TOI) mask of left and right SLF was created using John Hopkins University ICBM-DTI-81 white matter labels atlas (Mori *et al.*, 2008; <http://cmrm.med.jhmi.edu/>) and further masked with the group WM skeleton. To minimize any effects due to distortion of diffusivity measures through nonlinear registration of individual WM maps to the common WM skeleton in TBSS, the TOI masks were back-projected into each subject's native space and used to extract mean values for each diffusivity measure.

fMRI Acquisition and Analysis.

(EPI) sequence (93 axial slices, TR = 3000ms, TE = 30ms, flip angle = 90°, FOV = 192mm, voxel size = 2.5mm³, matrix = 76 x 76). Brain activation was assessed using the blood oxygenation level dependent (BOLD) effect (Ogawa *et al.*, 1990) with optimal contrast. For functional analysis, T2*-weighted images were preprocessed with Statistical Parametric Mapping software (SPM8; <http://www.fil.ion.ucl.ac.uk/spm>); specifically, they were realigned to a mean image for head-motion correction, spatially normalized into a standard stereotaxic space with voxel size of 2 mm³, using the Montreal Neurological Institute (MNI) template, and spatially smoothed with a 6-mm full width half maximum Gaussian kernel.

The procedure of the fMRI analysis was threefold. First, we conducted a seed-based FC-behaviour analysis in which we delineated the working memory network by determining areas of the brain in which the BOLD response was correlated with that of the seed regions (*i.e.*, its functional connectivity) and examined whether activity in this network correlates with two behavioural variables: accuracy scores (hits – false alarms) and reaction times (hits) on each of the n-back condition. Here we tested the hypothesis that the relation between FC in the working memory network and behavioural performance would differ between the two groups and that older adults would recruit a compensatory network. Second, we examined the relation between age-related changes in FC of the task-related network and structural changes in gray matter. For this purpose, we conducted a seed-based FC-GM analysis in which the BOLD response of the seed regions was correlated with the BOLD response of the rest of the brain and with individual values of cortical volume of bilateral IPL and MFG. Here we tested the hypothesis that age-related compensatory recruitment would be associated with greater GM volume in key working memory areas. Finally, we investigated the relation between age-related changes in FC of the

which the BOLD response of the seed regions was correlated with the BOLD response of the rest of the brain and with individual measures of white matter integrity (FA, AD, and RD) from bilateral SLF. Here we tested the hypothesis that age-related compensatory recruitment would be associated with greater WM integrity in frontoparietal WM pathways.

All covariance maps were statistically analyzed using a multivariate analytical technique called Partial Least Squares (PLS; McIntosh, Chau, & Protzner, 2004; McIntosh *et al.*, 1996; for a detailed tutorial and review of PLS, see Krishnan *et al.*, 2011), as implemented in PLS software (http://research.baycrest.org/pls_software) running on MATLAB Version 2013A (The MathWorks Inc.). PLS is designed to identify significant whole-brain activity patterns related to task demands, measures of behavioural or anatomical covariates, or activity in a given “seed” region. Activity patterns are assessed across all brain voxels together, which is in contrast to mass-univariate analyses that consider each voxel separately. PLS analysis uses singular value decomposition (SVD) of a single matrix that contains all participants’ data to find a set of latent variables (LVs), which are mutually orthogonal dimensions that reduce the complexity of the data set. In other words, PLS does not force contrasts but rather decomposes the data to maximize the amount of covariance of an LV with respect to the experimental conditions. Thus, akin to Principal Component Analysis (PCA; *e.g.*, Friston, Frith, & Frackowiak, 1993), PLS enables one to differentiate the degree of contribution of different brain regions associated with task demands, behavioural or anatomical covariates, or functional seed activity. Each LV consists of a singular image of voxel saliences (*i.e.*, a spatiotemporal pattern of brain activity), a singular profile of task saliences (*i.e.*, a set of weights that indicate how brain activity in the singular image is related to the experimental conditions, functional seeds, or

accounted for by the LV).

The significance of each LV is assessed by a permutation test, which determines the probability that a singular value from 500 random resamplings of the data is larger than the initially obtained value (McIntosh *et al.*, 1996). In addition to the permutation test, a second and independent step is to determine the reliability of the saliences (or weights) for each brain voxel that characterizes a given spatiotemporal pattern identified by the LVs. To do so, the standard error of each voxel's salience on each LV is estimated by 100 bootstrap resampling steps (Efron & Tibshirani, 1985). Peak voxels with a bootstrap ratio (BSR; *i.e.*, salience/standard error) > 3.0 were considered to be reliable, as these approximate $p < 0.01$ (Sampson *et al.*, 1989). Because extraction of the LVs and corresponding brain images is done in a single analytic step, no correction for multiple comparisons is required.

Results

Behavioural Performance.

Both the mean accuracy (hits – false alarms) and mean reaction time (RT) for hits differed significantly between the two groups, with young adults being significantly more accurate (1-back: $M = 0.97$, $SD = 0.04$; $t_{23} = 4.04$, $p < 0.001$; 2-back: $M = 0.86$, $SD = 0.08$; $t_{23} = 2.06$, $p = 0.04$) than older adults (1-back: $M = 0.87$, $SD = 0.11$; 2-back: $M = 0.78$, $SD = 0.13$), as well as faster (1-back: $M = 558$, $SD = 138$; $t_{23} = 5.44$, $p < 0.001$; 2-back: $M = 628$, $SD = 209$; $t_{23} = 4.91$, $p < 0.001$) than older adults (1-back: $M = 729$, $SD = 183$; 2-back: 803 , $SD = 266$).

Functional Connectivity & Behaviour Analysis.

network and their relation to behavioural performance on the n-back task. This analysis yielded two significant LVs. The first LV accounted for 64% of covariance in the data and delineated a bilateral but strongly left-lateralized working memory network (**Fig 1** and **Table 1**). In older adults, this network was functionally connected to both FP nodes during both n-back conditions and did not show modulation of FP activity with increased load. In young adults, however, during the low-load condition, this network was strongly functionally connected to IPL but not to MFG, suggesting a lack of necessity for frontal recruitment under low cognitive load. Young adults engaged MFG strongly only during the high-load condition, in conjunction with a significant decrease in connectivity to IPL (as confirmed by the Fisher r-to-z transformation that yielded a significant difference in IPL connectivity between 1-back and 2-back at $p < 0.05$). These results demonstrate dedifferentiation on the network level: young adults show differences in FC that are dependent on the degree of cognitive load, whereas older adults show no differences in load-related connectivity.

The behavioural covariates revealed differences in how FC in the working memory network related to performance. In young adults, accuracy scores positively correlated with activity in the working memory network during the high-load condition only, showing that more accurate young adults engaged this FP network more strongly than less accurate young adults when cognitive load was increased. Older adults did not show any significant correlation between activity in the working memory network and accuracy. However, older adults showed a positive correlation between RT and activity in the working memory network under the low-load condition, showing that slower older adults recruited the FP network more strongly than faster older adults did. Young adults, on the other hand, showed a negative correlation with RT during

to IPL under low cognitive load. Thus, unlike in their older counterparts, increased cognitive load was associated with increased FC to frontal areas and better performance in young adults¹.

[Insert Figure 1 & Table 1 here]

The second LV accounted for 9% of covariance in the data and delineated a network of bilateral frontal and right FP areas, which were functionally connected to left MFG but not left IPL (**Fig 2** and **Table 2**). This network was exclusively recruited by older adults during the high load condition. Activity in this network correlated positively with accuracy and RT (*i.e.*, the more accurate, but slower older adults recruited this network more strongly), suggesting a compensatory recruitment of alternate brain circuitry under a high cognitive load.

[Insert Figure 2 & Table 2 here]

Functional Connectivity & WM Analysis.

The FC-WM analysis assessed the relation of age-related alterations in FC of the task-related network and the integrity of WM microstructure in bilateral SLF. The analysis revealed two significant LVs, one related to correlations between FA values and activity in the working memory network (**Fig 3**), and the other to correlations between FA and AD values, and activity in the compensatory network (**Fig 4**, lower left graph). No significant correlations were found for RD values. Both LVs reflected significant covariance patterns only during the high load condition. In young adults, activity in the working memory network correlated positively with FA values, reflecting the importance of more intact WM microstructure in bilateral SLF for

¹ The pattern of functional connectivity remained the same (*i.e.*, a lack of parietofrontal modulation with increased cognitive load in old adults) when the two groups were equated behaviourally (n = 13 per group; young: 1-back: M = 0.95, SD = 0.04; 2-back: M = 0.85, SD = 0.07; old: 1-back: M = 0.95, SD = 0.04; 2-back: M = 0.86, SD = 0.09; *ps* > 0.1).

the compensatory network correlated positively with FA values and negatively with AD values, suggesting that those older adults who have more intact WM microstructure and less axonal damage recruit the compensatory network more strongly.

Functional Connectivity & GM Analysis.

The FC-GM analysis assessed the relation of age-related alterations in FC of the task-related network and GM volume of bilateral MFG and IPL. The analysis revealed one significant LV, related to correlations between GM volume and activity in the compensatory network shown only by older adults during the high load condition. Activity in the compensatory network correlated positively with GM volume in right IPL and negatively with GM volume in bilateral MFG (**Fig 4**, upper left graph). These results suggest that the structural integrity of the right IPL may play a critical role in the ability to recruit the compensatory functional network.

[Insert Figures 3 & 4 here]

Discussion

The current study examined the relations among age-related changes in FC of the working memory network, structural integrity, and performance. Our results demonstrate that with increased cognitive load (i) unlike young adults, older adults fail to modulate the strength of FC in the working memory network with increased cognitive load but (ii) recruit a compensatory network to improve performance. Furthermore, our findings demonstrate an association among structural integrity, functional activity, and behaviour in both young and older adults. Young adults showed an association between FC in the working memory network and WM

compensatory network, more intact WM microstructure, less axonal damage in bilateral SLF, and larger IPL volume in the right hemisphere.

Absence of Load-Dependent Modulation/Dedifferentiation

Our first finding provides evidence for dedifferentiation at the network level. Unlike young adults who modulated frontoparietal connectivity during working memory processing and strengthened FC to anterior areas with increased cognitive load, older adults failed to show such load-dependent frontoparietal modulation. Instead, FC between the frontoparietal nodes of the working memory network of older adults was equally strong, regardless of task demands. These findings align with the idea that older adults recruit more processing resources at lower levels of cognitive load, and show relative decreases in neural activity at high levels of cognitive load, as their available resources have reached their limit (Reuter-Lorenz & Cappell, 2008). Although increases in activity in existing functional networks relative to young adults have been interpreted as compensatory recruitment (Cabeza *et al.*, 2002; Persson *et al.*, 2004), the absence of behavioural improvement in our data does not support this interpretation. Rather, our findings are consistent with the idea of dedifferentiation, and show that the neural signature of the different load-dependent processes becomes less distinct (Grady, 2008; Li *et al.*, 2001). Previous studies found similar age-related reductions in neural sensitivity to different stimulus categories in visual perception (Burianová *et al.*, 2013; Carp *et al.*, 2010a, 2010b; Park *et al.*, 2004; Schiavetto *et al.*, 2002), memory processing (Carp *et al.*, 2010a, 2010b; St-Laurent *et al.*, 2011), and auditory processing (Grady *et al.*, 2011), as well as in amplitude differences between young and older adults that suggest age-related dysregulation of frontal executive functions that may lead to greater exertion of executive control than needed (Dirnberger *et al.*, 2010). Together with

working memory processes takes place in both frontal and parietal cortices, and that rather than being a strictly regional phenomenon, dedifferentiation in older adults can also occur at the network level.

Compensatory Recruitment

In young adults, behavioural performance under high cognitive load covaried with the strength of FC in the working memory network, meaning that young adults who performed more accurately engaged the network more strongly. Older adults, on the other hand, did not show such a relation. Instead, older adults' accurate performance was related to the recruitment of an additional brain network, functionally connected to left MFG. This network consisted predominantly of right prefrontal regions and the right IPL. The specificity of this functional network and its relation to accuracy in only the older adults provides evidence for compensation, which is defined as the recruitment of additional neural resources, which are directly related to improved performance (Grady *et al.*, 1994). In addition, whilst connectivity between left MFG and right IPL of the compensatory network strengthened, the functional connection between left MFG and left IPL disappeared. This finding aligns with the argument that age-related compensatory recruitment may be utilized to counteract altered processing in domain-specific areas (Burianová *et al.*, 2013; Davis *et al.*, 2008; Grady *et al.*, 2002; Schiavetto *et al.*, 2002), *i.e.*, the working memory network, and extends this notion to suggest that compensation may also involve functional rerouting to homologous anterior and posterior regions (*i.e.*, right prefrontal cortex and right IPL).

Interestingly, whilst the compensatory recruitment of the right hemispheric brain regions related to improved accuracy on the working memory task, it also correlated with slower reaction

provided by the partial compensation hypothesis (de Chasteine *et al.*, 2011), which argues that additional brain regions are recruited to aid older adults in accomplishing the task *because* the existing neural structures that subserve a cognitive process are less efficiently used. In our study, the lack of efficiency in the working memory network is evidenced by the age-related dedifferentiation of load-dependent conditions. However, whilst the additional recruitment may lead to more accurate performance on the task and hence be compensatory, it does not improve the efficiency of the existing neural structures, potentially yielding a more distributed network, at the cost of reaction time (Garrett *et al.*, 2011).

Relations Among Structure, Function, and Behaviour

Our findings revealed that under high cognitive load the strength of FC in the working memory network of young but not older adults was associated with higher FA in bilateral SLF. In older adults, a similar structure-function-behaviour relation was identified in the compensatory network, where higher FA and lower AD in bilateral SLF were associated with stronger FC under high cognitive load. FA is considered to be a general marker of WM integrity and nonspecific marker of microstructural change, most likely reflecting coherence within a voxel and fiber density (Alexander *et al.*, 2007; Beaulieu, 2002), whereas AD is considered to be a more specific marker of axonal damage or loss (Sun *et al.*, 2006). Conjoint analysis of multiple measures of white matter integrity has been argued to yield a more comprehensive picture of different elements of WM microstructure (Assaf & Pasternak, 2008); however, the interpretation of the neurobiological mechanisms reflected in the interaction of FA and AD is complicated by many variables. Different diffusivity patterns of age-related differences have been reported and shown to be region-specific (Bennett *et al.*, 2010; Burzynska *et al.*, 2010), but the general trend

specific measures of diffusivity (*e.g.*, Sullivan *et al.*, 2006, 2008; Zahr *et al.*, 2009). Although a decrease in FA accompanied by a decrease in AD have been reported in secondary Wallerian degeneration (Pierpaoli *et al.*, 2001), decreases in FA accompanied by increases in AD have been interpreted as reflecting higher extracellular volume fraction, lower membrane density, and an increase in axonal spacing as a result of axonal loss (Sen & Basser, 2005). Together with the brain-behaviour findings, which show that activity in the working memory and compensatory networks predicts performance in young and older adults, respectively, our results provide evidence that both cognitive performance and cortical connectivity depend on the microstructural integrity of white matter. Our results further suggest that the compensatory mechanism utilized by older adults is influenced by greater structural integrity and, more specifically, less axonal damage in bilateral SLF. These findings contribute to the limited, yet growing body of evidence that shows an association between better WM integrity, brain activation, and cognitive performance in older adults (Burzynska *et al.*, 2013; Chen *et al.*, 2009; Davis *et al.*, 2009; Lockhart *et al.*, 2012).

In addition to white matter integrity, our results show that the strength of FC in the compensatory network was associated with lower MFG volume bilaterally, but with higher IPL volume in the right hemisphere, suggesting that the structural integrity of the right posterior parietal region may be critical in the ageing brain's ability to recruit additional prefrontal regions for compensation. Recent studies show a relation between gray matter thinning and reductions in functional activation (Thomsen *et al.*, 2004), as well as a more specific negative correlation between MFG volume and frontoparietal activation during memory retrieval in older adults (Rajah *et al.*, 2011). Together with the results of our study, the findings of the aforementioned

age-related differences in brain structure may mediate changes in task-related functional connectivity and cognitive performance. Specifically, we propose that intact brain structure may play a biologically permissive role in functional compensation (Murphy & Corbett, 2009).

In conclusion, our findings show that whilst ageing is associated with dedifferentiation at the network level, greater structural integrity of both white and gray matter in and between relevant cortical regions are critical for the functional recruitment of a compensatory network, leading to improved accuracy on the working memory task. These results imply that task-related changes in functional networks in general rely on the properties of structural connections and that the underlying changes in structural integrity are related to changes in FC and performance on cognitive tasks. Future investigations of neural plasticity – age-related or otherwise – should continue to explore the interconnectedness of structure, function, and behaviour further, as many outstanding issues of how age-related differences in brain activation are related to other factors, *e.g.*, brain structure, remain.

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FIG 1. FC-Behaviour Results: LV1. *Right* – a pattern of whole brain activity in the working memory network; *Left* – correlations between activity in left MFG, left IPL, reaction times and accuracy during 1-back (*Top*) and 2-back (*Bottom*) conditions, as well as activity in the regions of the working memory network. Error bars denote 95% confidence intervals for the correlations calculated from the bootstrap procedure. All reported regions have $BSR \geq 3.0$ and cluster size ≥ 100 voxels. MFG = middle frontal gyrus; IPL = inferior parietal lobule; RT = reaction time; ACC = accuracy.

FIG 2. FC-Behaviour Results: LV2. *Top* – a pattern of whole brain activity in the compensatory network; *Bottom* – correlations between activity in left MFG, left IPL, reaction times, and accuracy during the 2-back condition, as well as activity in the regions of the compensatory network. Error bars denote 95% confidence intervals for the correlations calculated from the bootstrap procedure. All reported regions have $BSR \geq 3.0$ and cluster size ≥ 100 voxels. MFG = middle frontal gyrus; IPL = inferior parietal lobule; RT = reaction time; ACC = accuracy.

FIG 3. Structure-Function Relations in the Working Memory Network. *Right* – a pattern of whole brain activity in the working memory network; *Left* – correlations between fractional anisotropy in bilateral SLF and activity in the regions of the working memory network during the 2-back condition. Error bars denote 95% confidence intervals for the correlations calculated from the bootstrap procedure. All reported regions have $BSR \geq 3.0$ and cluster size ≥ 100 voxels. SLF = superior longitudinal fasciculus.

FIG 4. Structure-Function Relations in the Compensatory Network. *Right* – a pattern of

GM volume of bilateral MFG and IPL and activity in the regions of the compensatory network during the 2-back condition (*Top*); and between AD and FA in bilateral SLF and activity in the regions of the compensatory network during the 2-back condition (*Bottom*). Error bars denote 95% confidence intervals for the correlations calculated from the bootstrap procedure. All reported regions have $BSR \geq 3.0$ and cluster size ≥ 100 voxels. GM = gray matter; WM = white matter; MFG = middle frontal gyrus; IPL = inferior parietal lobule; HEM = hemisphere; L = left; R = right; AD = axial diffusivity; FA = fractional anisotropy.

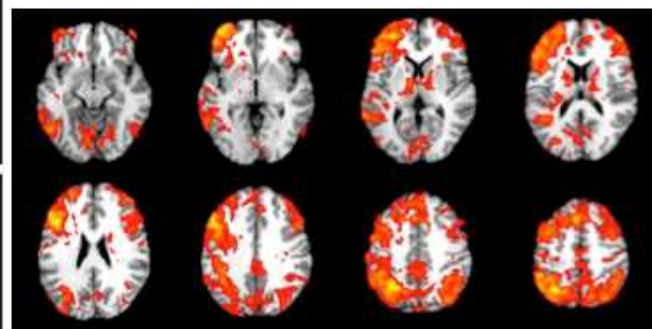
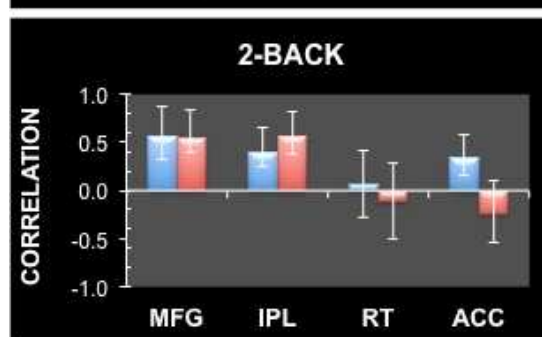
Working Memory Network						
Region	Hem	BA	MNI Coordinates			Ratio
			<i>x</i>	<i>y</i>	<i>z</i>	
Middle Frontal Gyrus	L	9/46	-48	18	30	16.75
	R	9/46	52	28	30	8.26
Middle Frontal Gyrus	L	10	-40	44	18	13.53
	R	10	46	46	20	12.47
Premotor Frontal Gyrus	L	6	-30	14	56	12.78
	R	6	38	14	54	9.07
Medial Frontal Gyrus		8	-4	24	44	14.60
Inferior Parietal Lobule	L	40	-48	-42	46	12.89
	R	40	46	-42	48	9.53
Superior Parietal Lobule	L	7	-30	-62	50	13.81
	R	7	38	-60	46	8.06
Precuneus	L	7	-6	-64	56	9.41
	R	7	32	-70	44	10.19
Posterior Cingulate Gyrus		31	4	-36	28	8.09
Thalamus	L		-10	-8	10	9.48
	R		12	-10	10	6.80
Fusiform Gyrus	L	37	-46	-56	-6	12.23
	R	37	46	-58	-8	6.15
Cerebellum	L		-24	-60	-24	9.18
	R		30	-68	-24	9.28

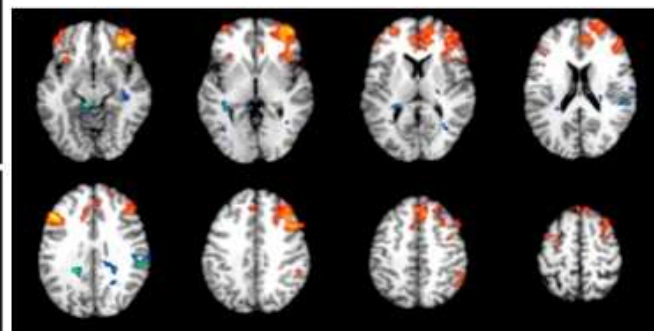
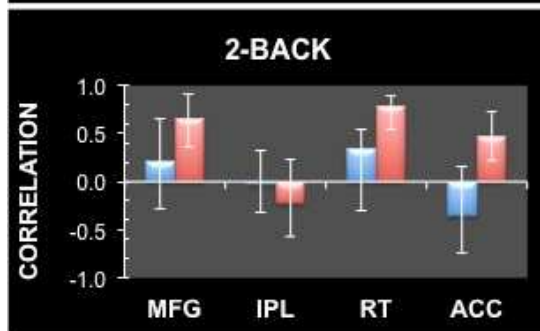
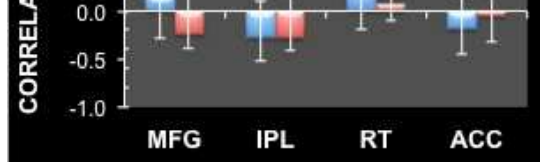
Abbreviations: **Hem** = hemisphere; **BA** = Brodmann's Area; **R** = right; **L** = left; **Ratio** = salience/SE ratio from the bootstrap analysis; *x* coordinate = right/left; *y* coordinate = anterior/posterior; *z* coordinate = superior/inferior.

Compensatory Network

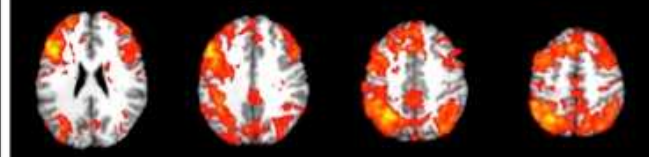
Region	Hem	BA	MNI Coordinates			Ratio
			<i>x</i>	<i>y</i>	<i>z</i>	
Inferior Frontal Gyrus	L	47	-32	20	-12	5.81
	R	47	26	24	-12	4.45
Frontal Pole	L	10	-34	60	-4	4.81
	R	10	44	56	0	7.29
Medial Frontal Gyrus		10	10	54	12	7.39
Superior Frontal Gyrus	R	10	20	50	24	6.52
Medial Frontal Gyrus		8	6	30	44	6.29
Middle Frontal Gyrus	L	9/46	-48	18	30	5.10
	R	8	40	18	50	6.05
Inferior Parietal Lobule	R	40	52	-56	44	5.63

Abbreviations: **Hem** = hemisphere; **BA** = Brodmann's Area; **R** = right; **L** = left; **Ratio** = salience/SE ratio from the bootstrap analysis; *x* coordinate = right/left; *y* coordinate = anterior/posterior; *z* coordinate = superior/inferior.



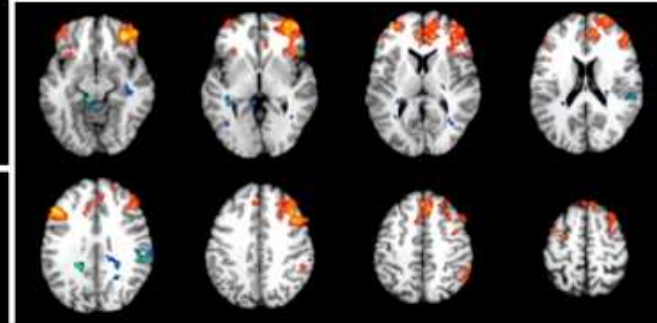
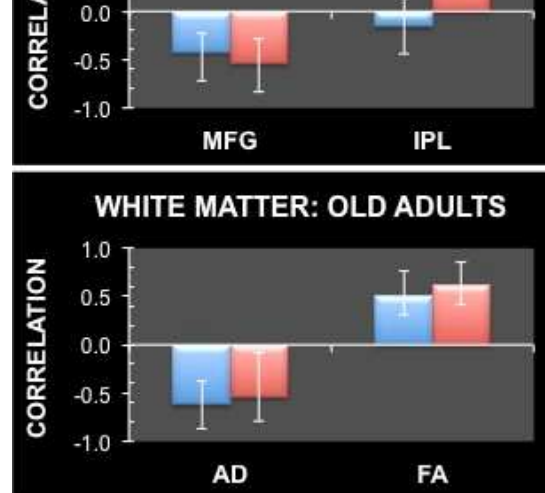


YOUNG
OLD



YOUNG
OLD

ACCEPTED MANUSCRIPT



LEFT HEMISPHERE

RIGHT HEMISPHERE

functional modulation due to cognitive load. > We report age-related dedifferentiation and compensation related to both brain function and structure. > These findings suggest a biologically permissive role of intact brain structure in functional compensation.

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